Chapter

New Developments in Behavioral Pharmacology

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Abstract

Behavioral pharmacology research has been a cornerstone in the understanding of the processes that underlie the behavior of living organisms as well as the biological basis of the behavioral, emotional, and cognitive disorders that affect humans. The findings in this area have helped to explore the potential therapeutic effects of several substances for the treatment of the mentioned disorders. The present chapter brings an extremely brief introduction to this vast area. First, we try to put in context behavioral pharmacology and its relevance and then show some brief examples of how this discipline has developed over the years. Second, we review the concept of a "research model" in preclinical behavioral pharmacology, given the importance of animal models and tests in this area, followed by a brief review of the recent advances using zebra fish as a valuable tool of research. Third, more specific examples are aborded, such as the findings on sleep disorders and those related to sexual hormones and menopause.

Keywords: behavioral pharmacology, psychopharmacology, psychoactive drugs, behavioral models

1. Introduction

Every time academics talk about the evolution of human societies and the advance of humanity, language is always mentioned, followed by different pieces of technology that allowed us to change the world. Few times, medicine is mentioned, and within the same area of knowledge, pharmacology is even more frequently omitted. But without the development of pharmacology as a science founded in systematic research, the capacities of medical sciences and therapeutics would be very limited. Knowledge in pharmacology allows us to understand that there exist chemical substances with very specific structures and properties which, in controlled doses, can interact with the normal physiology of our organism in order to produce effects that improve our health, known as therapeutic effects; but if the doses are insufficient or excessive, the effects will be useless or harmful (toxic), respectively [1]. These substances responsible for the actions of medicines are named as active compounds.

Most of the active compounds used in medicine were consumed together with the organism which contained them, most frequently plants. As chemistry advanced, scientists succeed in isolating these compounds and described their chemical structure. In consequence, laboratories started to synthesize these

substances and others with a similar structure that should be tested in research laboratories before using them to treat diseases in humans [2].

Nowadays, pharmacological research has grown beyond treatments for infectious agents, covering diseases related to the alteration of the normal functioning of the central nervous system (CNS). There are medications to treat disorders such as depression, anxiety, chronic pain, attention deficit and hyperactivity disorder, epilepsy, and Parkinson's disease, and new drugs are desperately sought to stop Alzheimer's disease. On the other hand, one of the most important current health problems is related to the addictive behaviors triggered by the consumption of certain substances and the side effects of these addictions: respiratory and cardiovascular diseases in the case of tobacco, metabolic diseases in the case of alcoholism and addictive consumption of refined sugars, infectious diseases in the case of injected drugs, and many others that are not mentioned here. Without losing sight of the fact that addiction is itself a disease of the nervous system with devastating effects *per se* on the patient's quality of life. In several countries, prescription of different therapeutic agents acting on the CNS to treat psychiatric disorders, such as antidepressants, antipsychotics, and stimulants, has increased [3, 4] as in the case of methylphenidate and amphetamines in different countries such as United States [5] and the Netherlands [6]. The same way, antidepressant users have increased markedly around the world in countries such as Norway, Sweden, and Denmark [7], among others. Additionally, the use of different substances of abuse such as tobacco [8] and marijuana has increased in the population [9]. Also, the development of new technologies and products has a significant impact on mental health as the discovery of Internet addiction [10] and the addictive consumption of refining sugar [11, 12], which impacts on the behavior of subjects. All these make important the continuous development of behavioral pharmacology in order to cope with the challenges in mental health.

2. Development of behavioral pharmacology

Behavioral pharmacology, also known as psychopharmacology, has developed as an interdisciplinary science that comprises fields such as neuroethology, neurochemistry, pharmacology and neuropharmacology, psychophysiology, neurophysiology, experimental analysis of behavior, and several other fields related to neurosciences [13]. Behavioral pharmacology is founded on systematic research with precise methods for assessing and interpreting the effects of chemical, hormones, and drugs on the behavior in humans and experimental animals in order to establish its potential as therapeutic agents or pharmacologic tools to explore how the brain functions and the underlying neurobiological mechanism of cognition, emotions, and behavior. Behavioral pharmacology must thus be an integral component of many neuroscience research programs [14].

In this sense, the development of behavioral pharmacology comprises the development of areas as pharmacology and psychology, experimental analysis of behavior, and recently neuroscience. For a historical review, see [14–16]. However, research in behavioral pharmacology can be summarized in: (1) the development of procedures to screen pharmacological agents for potential clinical effectiveness. (2) Perfecting behavioral techniques to explore the mechanisms of action of behaviorally active drugs and using these chemicals and drugs as tools for the analysis of complex behaviors (i.e., when drugs reinforce behavior and when drugs serve as discriminative stimuli) [16] (see **Table 1**). Therefore, drugs are not only a subject of study, because of its behavioral effects but are also a piece of technology that helps to elucidate how behaviors are controlled by living organisms.

Year	Description	Reference
1936	Selye H. described the impact of several types of adverse stimuli on animal health, in the form of a syndrome characterized by three phases: alarm, adaptation, and exhaustion, which can lead to death if stimuli are maintained. This syndrome was later named as the stress response which has been intensively studied and strongly associated with the impairment of brain function in animals or the development of mental disorders in humans	[17]
1972	The first study to administrate Delta-9-tetrahydrocannabinol in humans to test the effects on sleep patterns is carried out. The results show a decrease in sleep onset latency. To date, there are controversial results about the positive effects the cannabis on sleep quality	[18]
1977	The forced swim test is proposed as a behavioral tool to explore the effects of antidepressant drugs in rats and mice that are exposed to a stressful inescapable condition that triggers despair behavior (immobility)	[19]
1986	Elevated plus maze is developed as a tool to measure anxiety-like behaviors of the rat and test substances with potential anxiolytic effects	[20]
1988	Modafinil was prescribed for the first time for the treatment of narcolepsy and idiopathic hypersomnia in patients	[21]
2005	This study explored the behavioral and neuronal response to stress in ovariectomized rats (OVX). These rats were more sensitive to stress, which was associated with a low concentration of steroid hormones. This effect was prevented by restitution with 17-β estradiol	[22]
2006	Anxiety-like behavior is dependent on the post-ovariectomy time frame. At 12-week post-ovariectomy there is more anxiety-like behavior than a 3-week post-ovariectomy	[23]
2016	The first systemic review and meta-analysis that discuss the effects of the orexin agonist Suvorexant for the treatment of insomnia. Suvorexant improved some sleep parameters, but some adverse effects were reported	[24]
2019	In this study, it was identified that at 3-week post-ovariectomy appears anxiety-like behavior, but from 6-week post-ovariectomy in addition to anxiety-like behavior, also increases depression-like behavior in rats, supporting an experimental model of surgical post-menopause	[25]

Table 1.
Emblematic research in behavioral pharmacology.

3. Measuring behavior

Behavior is a biological property of organisms, which remarks on the significance of the study of drug-behavior interactions [15]. Maybe, a great example of the impact of behavior beyond psychology is the research by ethologists K. Lorenz, N. Tinbergen, and K. von Frisch, which focused on the analysis of behavior in several species including fish, insects, and birds, and the importance of which made them worthy of the Nobel price of medicine in 1973 "*for their discoveries concerning organization and elicitation of individual and social behaviour patterns*."

The first step in all behavioral sciences has been to define what is behavior; it could seem an easy task, but historically many different definitions of behavior have been used by scientists over the time, and even the knowing of a unique definition is elusive and may be useless for every different area such as psychology, ethology, and experimental analysis of behavior, among others; for review see [26, 27]. As mentioned before, one of the directions of behavioral pharmacology was the development of procedures to screen the effects of pharmacological agents on specific behaviors under controlled environments. This approach allows scientists to work with operational definitions of specific behaviors, for example, exploration can be

measured by scoring ambulation, rearing or nose approaching to an object; sexual behavior can be measured by conditioned place preference, number of mounts, latency and number of ejaculations. All these behaviors are normally studied under controlled environments that are designed specifically to the required behavioral display and every feature of the environment; the experimental subjects or chemical agents with probed effects on humans have been studied in this environment with the purpose of establishing these manipulations as models of a specific behavior (see **Table 2**) as spatial learning and memory, or models of specific pathologies behaviorally expressed as is the case of anxiety [28], depression [29], obsessive compulsive disorder [30], Parkinson [31], epilepsy [32] or addictive behaviors [33], and sleep deprivation [34], among others.

3.1 Behavioral models of brain disorders

Animals are used as proxies for human phenomena throughout the literature, and the exact definition of what constitutes a "model" can be confusing. In behavioral pharmacology, a field that intersects between psychology, neuroscience, and pharmacology [42], different uses are attributed to different epistemic operations and, as a consequence, to different definitions of validity [43, 44]. One of the most basic definitions is that by Paul Willner, which defined screening tests as those uses of animal behavior that are capable of discriminating between different drug effects (i.e., possess high predictive validity); behavioral bioassays as those uses of animal behavior that are capable of shedding light on the neural basis of normal behavior (i.e., possess high

Research area	Description
Hormone restitution therapy	This review discussed, 25 years ago, the importance of steroid hormones in the regulation of behavior and some psychiatry disorders; particularly depression associated with premenstrual syndrome and the transition to menopause. Also, it discusses some research about the role of hormone restitution therapy in ameliorating depression symptoms [35]
Sexual dimorphism	This review discusses preclinical and clinical research that show how hormones are involved in the sex differences in some psychiatric disorders like anxiety, and their interactions between fear, stress, and gonadal hormones [36]
Behavioral animal models	This research reviews the relevance of non-mammalian models in behavioral pharmacology with application in the development of biological psychiatry [37]
Behavioral model of menopause	This review highlights the importance of animal models of menopause in the understanding of neurobiological changes associated with the long-term absence of ovarian hormones. To then elucidate novel perspectives and interventions to improve the life quality in the menopausal women under a translational context [38]
Sleep and insomnia	This review describes the efficacy of new drugs in the treatment of insomnia such as melatonin, Remelteon, Tasimelteon, and Suvorexant, among others [39]
Hormones and behavior	This review discusses the influence of hormones on brain function and behavior, and integrate information to explain how the brain and the body communicate reciprocally via hormones and other mediators, and in ways that influence brain and body health but which can also accelerate diseases processes when the mediators of allostasis are dysregulated [40]
Addiction	A review of the most popular behavioral models for the study of addictions such as conditioned place preference and self-administration and new models to study behavioral addictions as gambling and exercise addiction [33]
Sleep disorders	This review describes the Pitolisant (Wakix®), first-in-class antagonist/inverse agonist of the H3 receptor for the treatment of narcolepsy with or without cataplexy [41]

Table 2.
Current topics in behavioral pharmacology.

face validity); and simulations as those uses of animal behavior that can inform on the etiology, pathophysiology, and treatment of human (mental) disorders (i.e., possess high construct validity). Further developments of this framework [45] advance the theory of validity, therefore improving the capability of researchers to evaluate animal models.

Screening tests show good predictive validity in that they are able to detect the effects of drugs, which are already known to have clinical efficacy; as a result, they are likely to be able to predict the effect of new drugs, which show similar biochemical or behavioral effects in the test [42, 43]. Examples include most uses of the tail suspension test and forced swim tests, which are commonly referred to as models of depression but actually do not simulate the etiological and pathophysiological aspects of human depression. When used without any further manipulations of the animal (i.e., lesions, genetic manipulations, or other stressors which are thought to be causally related to depression), these tests are good at discriminating drugs which act as serotonin reuptake inhibitors and reasonably good at predicting antidepressant efficacy. Since screening tests rely mostly on predictive validity, current approaches to modeling in behavioral pharmacology view them as limited. Moreover, producing models which show good construct validity in at least some domains (i.e., epidemiology, symptomatology and natural history, genetics, biochemistry, etiology, histological alterations, or endpoints) has been proposed as a way to indirectly increase predictive validity [46], as drugs which improve performance in a test that simulates at least some aspects of the target disorder.

Behavioral bioassays are tests that use nonhuman animals to try to understand the histological, electrophysiological, biochemical, and genetic bases of neurobehavioral functions [42, 43]. Usually, bioassays are used to understand normal functioning, instead of pathological alterations in these psychological processes. They rely on face validity—that is, how much performance in the test "resembles" the target human function. Of course, taken "as is," face validity runs a great risk of anthropomorphism, and the resemblance should not be sought at the topography level, but at the functional level [47]. For example, the elevated plus-maze, when used as a test *per se* (and not as an endpoint in a simulation), is interpreted as a behavioral bioassay of anxiety due to the functional role of thigmotaxis in rodent defensive behavior [48, 49]. Of course, this comparison only makes sense if we consider that anxiety is a normal mechanism that is associated with defensive behavior [50, 51]. Thus, the face validity of a test is only as good as our psychological/behavioral theory about a given function (i.e., anxiety, fear, memory, and attention, among others) [47].

Finally, simulations are tests, which use nonhuman animals to try to understand a human disorder from the point of view of etiology and pathophysiology [42, 43]. Most approaches to psychopathology currently frame disorders in a diathesis-stress theory [45], which assumes that vulnerabilities (general or specific; genetic, developmental, or temperamental) increase the probability of developing a specific disorder when the individual passes through general or specific stressors. In analogy, to develop a simulation of a mental disorder in a nonhuman animal, the vulnerabilities and stressors should be modeled, transforming an "initial organism" into a "vulnerable organism" and this latter into a "pathological organism," in which behavioral endpoints are assessed and biomarkers evaluated [44, 45]. From all senses of "behavioral model," the simulation is the one that better approaches the idea of modeling a disease [42, 44], but is also the more time-consuming. Moreover, to increase the construct validity of a simulation, aspects such as etiology and pathophysiology should be taken into consideration, but sometimes these aspects are unknown and are precisely what is under investigation [42]. Thus, high construct validity needs to be balanced against practical constraints, and therefore no behavioral simulations

with optimal characteristics exist [52]. In the next pages some examples of these "behavioral models" are described in order to introduce the present book.

4. Behavioral models in zebra fish

Under the framework discussed above for behavioral models, interesting approaches have appeared using non-rodent species. While mice and rats are still the most widely used model organisms in behavioral pharmacology [53], zebra fish (*Danio rerio* Hamilton 1822) come in an honorable third place, quickly "swimming into view" as a relevant model organism in this field [54]. The "classical" criteria for selecting a model organism in genetics and developmental biology—small size, fast (and external) development, easy reproduction, low cost, genetic tractability [55]—are present in zebra fish [37]. Moreover, other advantages are also described by zebra fish researchers: phylogenetic position; intermediate complexity in physiology and throughput; availability of tools to study neurocircuitry and to interfere in normal function (i.e., expression vectors, pharmacogenomic tools, and advanced microscopy); a productive community of researchers; and accumulation of significant data and methodological developments [37]. The combination of these characteristics suggested that zebra fish could be a suitable model organism in behavioral pharmacology.

Currently, very few true simulations exist in zebra fish, and most behavioral tests that are used to study psychiatric disorders in this species are actually screening tests or behavioral bioassays. This is a consequence of an extensive focus of the research in the field in the last 20 years on developing behavioral tests. This step, of course, was necessary to galvanize research in the field. Notable exceptions exist, but—as is the case with most initial work on using model organisms to study disorders and investigational treatments—these are still limited. However, past research has identified and allowed to control factors that affect zebra fish behavioral tests. Now it is clear how chemical properties of the water, illumination, number of fish per tank and routes of administration modify pharmacological effects. For example, administration by immersion is useful for chronic treatments but lacks a precise control of the doses absorbed [56], on the other hand, intraperitoneal administrations ensure the absolute control of doses but are not useful for chronic treatments due to the stress that produce [57]. Oral administration through drugs incorporated in the food is useful for chronic treatments and controlling the doses is easier than immersion [58], however chemical properties of the drug determine their ability to hold into the food until swallowed and oral metabolism must be considered. With the standardization of the proper protocols these factors can be controlled, and its effects limited so, behavioral pharmacology research with zebra fish is still a suitable and growing field.

The zebra fish light/dark test [59] and the novel tank test [60] are widely used to test the effects of different drugs on anxiety-like behavior in this species. These tests rely on natural preferences observed in the wild, and display excellent remission validity—that is, they are sensitive to drugs which affect anxiety in clinical settings, and not sensitive to drugs which do not affect anxiety [61]. As a result, these tests were used as screening tests to investigate new drugs, including drugs derived from natural products and plants, for example, refs. [62, 63]. These tests have also been used to study the neural mechanisms of anxiety-like behavior [64–68]. Thus, these tests can be used both as screening tests and as behavioral bioassays.

The behavior of adult zebra fish is more complex than the behavior of larvae, but its throughput is smaller. Throughput can be increased by testing larval behavior in microplates [69]. Light levels and stimuli can be delivered simultaneously to

many larvae at once, increasing throughput and reproducibility. For example, the photo-motor response (a stereotypic series of motor behaviors that are elicited by high-intensity light) is sensitive to a wide range of psychoactive drugs and able to predict mechanisms of action of drugs, which were previously not investigated in rodents [70]. A battery of assays has been proposed in larval zebra fish that is highly sensitive to antipsychotics and able to identify haloperidol-like compounds [71]. While suffering from the low face and construct validity these assays show very good predictive validity, and therefore are suitable as screening tests.

Examples of simulations can be found in the field of neurological disorders [72]. An interesting example is the generation of mutants with differences in genes known to be associated with diseases. In humans, mutations in the SCN1A gene, which encodes a voltage-gated sodium channel, causes Dravet syndrome, characterized by severe intellectual disability, impaired social development, and drug-resistant seizures. The scn1Lab mutant zebra fish displays spontaneous seizure-like electroencephalogram activity, convulsive-like motor patterns, and hyperactivity [73]. These mutants have been used to investigate drugs, which could be used to treat Dravet syndrome in human patients; drugs that affect the serotonergic system have been found to ameliorate the symptoms in the mutants [74], and suggest interesting avenues for human patients.

Now, we will review the role of behavioral pharmacology on a subject extensively explored in human trials: sleep.

5. Behavioral pharmacology and sleep disorders

Pharmacological treatment of sleep disorders is still partially known and not well understood. Currently, extensively pharmacological research is focused in two sleep disorders: insomnia and narcolepsy. Insomnia is defined as the individual's inability to fall asleep, manifested by a long latency to sleep onset and frequent nighttime awakenings experienced three times per week or more, for at least 1 month [75]. Insomnia causes emotional disturbances, impairs cognition, and reduced quality of life [76, 77]. Most epidemiologic studies have found that about one-third of adults (30–36%) report at least one symptom of insomnia, like difficulty initiating sleep or maintaining sleep [78]. Currently, benzodiazepines or Z-drugs (zopiclone, zolpidem, or zaleplon) are the first options to treat insomnia. These drugs act as positive allosteric modulators at the $GABA_A$ binding site, potentiating GABAergic inhibitory effects [79]. However, short-term or long-term treatment with these drugs has undesirable effects such as cognitive or memory impairment, the rapid development of tolerance, rebound insomnia upon discontinuation, car accidents or falls, and a substantial risk of abuse and dependence [39, 80, 81], which make necessary research on new potential therapeutic agents.

According to the new evidence-based clinical practice guidelines for the treatment of insomnia [75], new pharmacology agents for insomnia management are implemented (**Table 3**).

On the other hand, Type 1 narcolepsy (narcolepsy with hypocretin deficiency) is a chronic neurodegenerative sleep disorder caused by a deficiency of hypocretin-producing neurons in the lateral hypothalamus (LH). Hypocretin neurons are involved in the control of the sleep-wake cycle [87]. Treatment of narcolepsy is traditionally based on amphetamine-like stimulants that enhance dopaminergic release to improve narcoleptic symptoms. Nonetheless, a new group of drugs is arising as a forthcoming treatment of narcolepsy.

Pitolisant (Wakix®) is an inverse agonist of the histamine H3 auto-receptor that not only blocks the braking effect of histamine or H3 receptor agonists on

Drugs	Site of action	Therapeutic effect
Antidepressant (trazodone, mirtazapine, olanzapine, and quetiapine)	Agonists of the serotonin receptor 5-HT_{2A} and 5-HT_{2C}	Moderate improvement in subjective sleep Little improvement in sleep efficiency [82]
Antiparkinsonian ropinirole	Agonist of the dopamine receptor D2	Improvement in efficiency of sleep and total time slept [83]
Suvorexant	Antagonist of the orexin receptor	Improvement of sleep onset and subjective total slept time compared to placebo [84]
Ramelteon	Dual agonist of both MT1 and MT2 melatonin receptors	Improvement in latency to persistent sleep, total sleep time and sleep efficiency [85]
Diphenhydramine	Agonist of the histaminergic receptors	No clear beneficial impact on sleep [86]

Table 3.
New drugs used to insomnia management.

endogenous histamine release from depolarized synaptosomes but also enhances histamine release over the basal level (even at low nanomolar concentrations) in the structures as hypothalamus and cerebral cortex [88]. The administration of 20 mg/kg of Pitolisant promoted wakefulness, and decreased abnormal direct REM sleep onset in narcoleptic hypocretin knockout mice by enhancing histaminergic and noradrenergic activity [89]. Pitolisant seem a safe therapeutic option since doses of 120 mg once a day in the morning, that represent six times the therapeutic, doses did not produce adverse effects and plasma levels reduced at the end of the day, ensuring a lack of waking effect during the night [90]. Additionally, adverse effects due to metabolic drug-drug interaction are low since Pitolisant is metabolized by two distinct CYP_{450} isoforms. For example, the administration of 40 mg of Pitolisant together with 10 mg of Olanzapine to a group of healthy volunteers did not change drug plasma levels compared to only one drug administration [91].

6. Behavioral pharmacology of steroid hormones in a model of surgical menopause

Any chapter on behavioral pharmacology would be incomplete without a section reviewing the effects of certain hormones. Behavioral, emotional and affective states are influenced by plasma and brain concentration of steroid hormones in diverse organisms. Particularly, in nonhuman primates and humans there is significant sexual dimorphism respect to behavior and emotional states. Initially, the attributed properties of steroid hormones were related to the maintaining of secondary sexual characters and reproductive function, but some decades ago, it has been established that steroid hormones also influence behavior and some psychiatric disorders. Expression of anxiety- and depression-related behaviors depends on plasma and brain levels of steroid hormones; which in vulnerable subjects could predispose to development of some psychiatric disorder [92].

In humans, anxiety and depression symptoms are more frequent in women than men in a proportion of 3:1. These differences have been attributed to differences in the concentration of steroid hormones. Particularly in women, a high incidence of anxiety and depression symptoms has been identified during physiological states

characterized by low concentration of steroid hormones (i.e., estradiol, progesterone and their reduced metabolites) as naturally occur during premenstrual period, post-partum period, and transition to menopause [93, 94]. However, it also occurs when women are subjected to a surgical procedure to remove the ovaries (i.e., oophorectomy) with or without the uterus (i.e., hysterectomy), where an abrupt reduction in steroid hormones concentrations occurs [95] affecting behavioral response. Apparently, the significant reduction of steroid concentration produces anatomical, physiological, and neurochemical changes in the brain, that negatively impact on behavior, emotional, and affective states [96, 97].

Preclinical research with laboratory animals has made possible identify the behavioral and emotional changes associated with a reduced concentration of steroid hormones when rats are undergoing to an extirpation of both ovaries (i.e., ovariectomy), which increases vulnerability to stress that can be reverted by injection of severe doses of estradiol [22]. The long-term ovariectomy (> 8 weeks post-ovariectomy) is considered then as a surgical menopause model that explores the behavioral, neurobiological, emotional and affective changes associated with oophorectomy that occurs in women [98]. In the long-term ovariectomized rats display higher anxiety- and depression-like behavior in experimental models such as elevated plus maze and forced swim test, respectively. These behavioral changes are correlated with a reduced neurochemical activity on serotonergic, noradrenergic, dopaminergic, and GABAergic pathways; in addition to a reduction in the number of dendritic spines and neuronal activity in some brain structures (i.e., hippocampus, amygdala, lateral septum, prefrontal cortex, among others). Through behavioral analysis is possible identifying the gradual changes associated with surgical menopause in rats. It was observed that after 3-week post-ovariectomy, rats showed high anxiety-like behavior (i.e., there is a reduction of exploration of the open arms) in the elevated plus maze with respect to cycling rats with intact ovaries, but after 6-week post-ovariectomy, additionally to anxiety-like behavior, rats also displayed high depression-like behavior in the forced swim test (i.e., increase in the total time of immobility), which negatively correlates with the Fos-immunoreactive cells in limbic brain structures such as the lateral septal nucleus [25]. The behavioral and neurochemical characterization of long-term ovariectomy allows the pharmacological research of different substances that could be potentially relevant to the development of pharmacological therapies to ameliorate anxiety and depression symptoms that occur during natural or surgical menopause.

As mentioned before, anxiety-like behavior is dependent on the post-ovariectomy time frame in rats. After 12-weeks post ovariectomy rats show high anxiety-like behavior respect to rats at 3-weeks post-ovariectomy in the burying behavior parading. This high anxiety-like behavior is reduced after injection of 1–2 mg/kg diazepam, a typical anxiolytic benzodiazepine drug [23]. Similarly, i.p. injection of 0.5 and 1 mg/kg phytoestrogen genistein (a secondary metabolite obtained from soybeans) significantly reduces anxiety-like behavior in rats at 12-week post-ovariectomy in the light/dark behavioral paradigm through action on the estrogen receptor-β [99, 100]. Additionally, s.c. injection of 0.9 or 0.18 mg/kg genistein exerts similar anxiolytic-like effects in the elevated plus maze than 17β-estradiol in rats subjected to surgical menopausal model. This is consistent with clinical observations that estradiol reduces anxiety symptoms associated with natural and surgical menopause, and additionally supports the potential use of phytoestrogens as an alternative therapy to ameliorate emotional symptoms associated to menopause.

Research in behavioral pharmacology has contributed to the study of pharmacological actions of natural products. In rats at 12-weeks post-ovariectomy, 50 mg/kg by oral

rout of the aqueous crude extract of *Montanoa tomentosa*, a Mexican plant traditionally recommended for the treatment of anxiety and other illness of women, reduces anxiety-like behavior in the elevated plus maze [101]. Said actions have been related with pharmacological actions on the $GABA_A$ receptors [102]. Additionally, secondary metabolites from plants, for example, the flavonoids are reported with anxiolytic properties in behavioral models in rats. In this way, 2 and 4 mg/kg, i.p., of the flavonoid chrysin produces anxiolytic-like effects in rats with surgical menopause subjected to the elevated plus maze and the light/dark test [103]; the said effects were produced through action on the $GABA_A$ receptor because the pretreatment with 1 mg/kg picrotoxin, a noncompetitive antagonist of the $GABA_A$ receptor, cancels the anxiolytic-like effect of chrysin.

7. Conclusion

As mentioned before, behavioral pharmacology is an interdisciplinary field. The present chapter tried to reflect briefly the essence of behavioral pharmacology through an anecdotical review of its developments in areas familiar to the authors. All findings mentioned above underline the importance of the research in behavioral pharmacology on the understanding of the neurobiology of different disorders and the mechanism of action of drugs used to treat such disorders, and at the same time, provide a perspective on the current research done in this growing area, which is and will be a cornerstone in the understanding of human behavior and mental health.

Conflict of interest

The authors do not have any conflict of interest.

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